



UNIVERSITY OF GOTHENBURG

INTESTINAL TRANSPLANTATION EXPERIMENTAL AND CLINICAL STUDIES

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Göteborgs Universitet kommer att offentligens försvaras i Hjärtats Aulan, Sahlgrenska Universitetssjukhuset fredagen den 29:e januari 2010, kl. 09,00

av

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Leg.läkare

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Avhandlingen baseras på följande arbeten:

- I. **Oltean M**, Joshi M, Herlenius G, Olausson M. **Improved intestinal preservation using an intraluminal macromolecular solution: evidence from a rat model.** Transplantation, *In press*
- II. **Oltean M**, Pullerits R, Zhu C, Blomgren K, Hallberg EC, Olausson M. **Donor pretreatment with FK506 reduces reperfusion injury and accelerates intestinal graft recovery in rats.** Surgery, 141:667-677, 2007
- III. **Oltean M**, Zhu C, Mera S, Pullerits R, Mattsby-Baltzer I, Mölne J, Hallberg EC, Blomgren K, Olausson M. **Reduced liver injury and cytokine release after transplantation of preconditioned intestines,** J Surg Res, 154:30-37, 2009
- IV. **Oltean M**, Herlenius G, Gäbel M, Karlsson-Parra, A, Olausson M. **Sustained elevations in plasma resistin, an inflammatory adipokine, after clinical intestinal transplantation.** *Manuscript*

Intestinal transplantation. Experimental and clinical studies

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ABSTRACT

Intestinal preservation-reperfusion injury may result in various degrees of mucosal injury. Intestinal preservation-reperfusion injury may result in various degrees of mucosal injury. Interestingly, the preservation injury is similar when using the current preservation solutions, which are given as a intravascular flush. An extensive mucosal injury may ultimately preclude the use of organs that require longer preservation time. The intestine lacks a noninvasive rejection marker, as in the case of liver or kidney transplantation. Several biomolecules have been suggested as biomarkers, yet their specificity is only partial.

Methods: Using a rat intestinal transplant model we studied the pharmacologic donor preconditioning and the intraluminal preservation with two different macromolecular solutions as means to decrease the intestinal preservation-reperfusion injury. We also investigated the impact of donor preconditioning on the ensuing systemic inflammatory response after transplantation. We analyzed resistin levels after clinical intestinal transplantation and seek to establish its significance and potential as rejection marker.

Results: Intraluminal introduction of low-sodium macromolecular solutions resulted in improved morphology after 8h and 14h of preservation compared with controls receiving only vascular flush with UW-solution. Moreover, intraluminal high-sodium solutions appear detrimental. These solutions also seem to influence differently the TJ conformation during preservation and delocalization of claudin-3 and ZO-1 was more prominent in intraluminal high-sodium solutions. Following transplantation, pretreated grafts showed accelerated repair and improved morphology. Pretreated grafts revealed reduced NF-kappaB activation after reperfusion and subsequently blunted ICAM-1 expression and PMN sequestration. Pretreated graft recipients had milder liver injury and lower levels of the proinflammatory cytokines TNF-alpha, IL-1beta and IL-6 than recipients of untreated grafts.

Resistin levels were studied in seven patients receiving intestinal grafts. Resistin increased in all patients compared with controls and remained increased even during uneventful course. Resistin did not correlate with CRP, BMI, procalcitonin or WBC and it varied greatly between patients.

Conclusions: Preservation-reperfusion injury may be mitigated by the intraluminal introduction of macromolecular solutions or by donor pretreatment with FK506 before graft harvesting. FK506-pretreated grafts trigger a lower remote organ injury and lower systemic inflammatory response. Plasma resistin levels greatly and were increased in all patients. However, the increase was unspecific and varied between individuals. Resistin appears unsuitable as rejection marker after intestinal transplantation.

Keywords: intestinal preservation, ischemia-reperfusion injury, tight junction, FK506, resistin,